To explore how these three pathogens activate unique patterns of gene transcription, Huang *et al.* studied the responses of cultured dendritic cells to molecules produced by these microbes. For example, lipopolysaccharide from the cell wall of *E. coli*, yeast cell wall–derived mannan, and viral double-stranded RNA activate the innate immune system through distinct receptors that recognize specific biochemical patterns. These microbial ligands triggered only a subset of genes induced by the whole live pathogen. Generally, the live pathogen was a more potent gene activator than its ligand. For example, 5 to 10 times more mRNA and protein of inflammatory cytokines (tumor necrosis factor–α, p40, and interleukins IL-12 and IL-10) were elicited by *E. coli* than by lipopolysaccharide. Curiously, in some cases the pattern of genes triggered by the microbial ligand failed to correlate with that induced by the intact pathogen; for example, the set of genes activated by yeast-derived mannan was more similar to that elicited by *E. coli* than by *C. albicans*. But what does all of this information really tell us?

In the case of cancer, microarray analysis of different tumors at different stages of malignancy has yielded information that could not be discerned by pathological examination. For example, gene arrays have been used to classify leukemias (*3*), breast cancers (*4*), and melanomas (*5*), and in some cases to predict the survival of cancer patients. An elegant gene chip study has shown that the signaling protein RhoC is essential for metastasis of melanomas (*6*). Such research is paralleled by studies of in vivo gene expression in microbial pathogens using several sophisticated approaches including in vivo expression technology (IVET) (*7*), molecular beacons (*8*), and terrain mapping (*9*). These techniques, combined with gene chip studies of immunologic responses to microbial pathogens and their ligands, are already yielding important functional information (*10, 11*).

The interaction between a pathogen and its host is clearly complex. It is one thing for the expression of 1000 genes to be altered by infection and neatly classified into families, but quite another to know which of these genes are crucial for host defense, and which promote microbial invasion, survival, and pathogenesis. Different pathogens (and their products), which presumably interact with different patterns of cell receptors, stimulate both common and unique signaling pathways and activate the expression of a number of different genes. The study of gene chip arrays is often referred to as "functional genomics," and classifying genes whose expression is altered on the array allows us to speculate about what these genes do.

But, which of the activated genes are crucial for protective immunity, which have little to do with the immune response, and which are involved in tissue injury? Array data narrow down the possibilities, and as such are enormously valuable, but annotations alone cannot answer these questions. Huang *et al.* did confirm in vitro that some of the cytokines produced by dendritic cells in response to *E. coli* were able to increase chemotaxis of neutrophils, key inflammatory cells. It remains to be determined whether these cytokines do the same in vivo.

How will functional genomics become functional? In a world of multiple genes and quantitative traits controlling complex phenomena, such as immunity to infection, how do we learn which genes count and which do not? And how will your automated health care provider of the future, analyzing a drop of your blood before a trip to an exotic destination, discern worrisome susceptibilities to nasty pathogens (and provide you with the appropriate therapeutic drug or vaccine)? Perhaps answering these questions will require reverting to the quaint hypothesis-driven, low-throughput approach once known as experimental biology.

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PERSPECTIVES: ASTRONOMY

Brown Dwarfs

John E. Gizis

Below about 75 times the mass of Jupiter (75 M_J), astronomical objects cannot achieve core temperatures hot enough for sustained nuclear fusion of hydrogen. These failed stars are called brown dwarfs. The hydrogen burning limit thus defines the cutoff between stars and brown dwarfs, but the term "brown dwarf" is usually also taken to refer to objects that form through collapse and fragmentation of an interstellar cloud (like stars) rather than originating in a circumstellar disk (like planets).

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It has long been expected that star formation will produce brown dwarfs, particularly because the time scales of brown dwarf formation are too short for hydrogen burning to be relevant. However, detection of brown dwarfs has proved difficult because they are very faint. Star and planet formation models have to account for the properties of these objects at the extreme low-mass end of the stellar mass distribution. Thanks to improved telescopes and detectors, the observational characterization of brown dwarfs is now well under way. But although models of the evolution of brown dwarfs are well developed, models of their formation are still in a preliminary state.

The first unambiguous brown dwarfs were discovered in 1995. Since then, hundreds have been identified in star-forming regions, young open clusters, and the field. Nearby, old brown dwarfs in the field have been identified with the Deep Near-Infrared Survey (DENIS), Two Micron All-Sky Survey (2MASS), and the Sloan Digital Sky Survey (SDSS). New spectral classification systems have been developed to characterize their properties (*1–4*). Over the course of 100 million to 10 billion years, an individual brown dwarf will evolve through spectral classes M (with an effective temperature $T_{eff} > 2200$ K), L (2200 K > $T_{eff} > 1400$ K), and T (1400 K > $T_{eff} > 700$ K) to as yet unobserved cooler states.

There is now wide agreement that brown dwarfs are numerous but not a substantial source of dark matter. Counts of brown dwarfs in the field, open clusters, and star-forming regions indicate that brown dwarfs represent a small (less than 15%) fraction of the stellar mass but a substantial fraction by number (*5*).

If the brown dwarf population is a result of the star formation process, it should share properties with stars. Many—if not most—stars are found in multiple systems, and the formation of circumstellar disks is also common. Some 20% of L dwarfs in the 2MASS survey turn out to be doubles when imaged with the Hubble Space Telescope. The brown dwarfs in these pairs are between 1 and 10 astronomical units (AU; 1 AU equals the Sun-Earth distance) apart, indicating that there are few wide brown dwarf–brown

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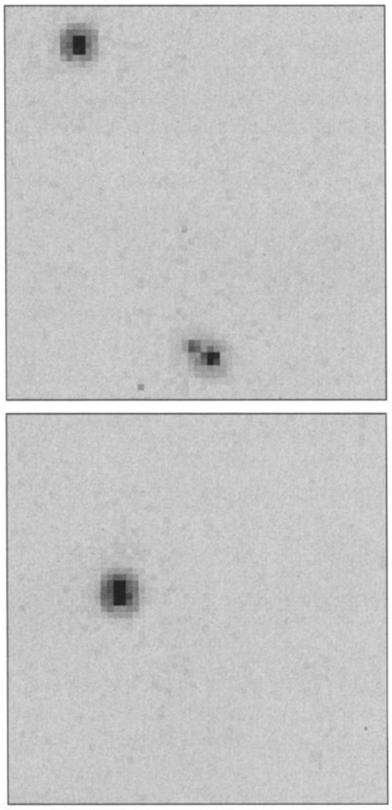
dwarf systems but many close doubles (see the figure) (*6*). Additional brown dwarf doubles are likely to be too close to be resolved.

The fraction of brown dwarfs found in multiple systems and the distribution of orbital separations are not identical with those of solar mass stars, but the observations are consistent with an extension of the properties of the lowest mass stars. Some widely separated brown dwarf companions to main sequence stars have also been detected. Furthermore, like stars, many very young brown dwarfs show evidence of disks (*7*, *8*). Whether these disks result in planetary systems is as yet unknown.



Hubble Space Telescope images of double brown dwarfs (*6*).

The basic structure and evolution of brown dwarfs are well understood, but many questions remain. First, characterization of the magnetic fields and magnetic activity of brown dwarfs is preliminary. Second, the x-ray coronae and Hα chromospheres so common among low-mass stars weaken and disappear around the hydrogen burning limit, but flares continue, at least in late-M spectral classes (*9*–*11*). Third, the properties of cool atmospheres are very difficult to calculate. Theoretical models predict dust formation in the atmosphere, and preliminary indications of weather variability due to dust clouds have been observed (*12*).

Studies of star-forming regions in Orion indicate that the brown dwarf sequence extends smoothly down to at least 5 to 8 M_J and possibly to lower masses (*13*, *14*). Extrasolar planetary systems with more massive (>7 M_J) components have been detected (*15*), indicating that the upper tail of planet formation and the lower tail of star formation overlap in mass. This overlap has created a dilemma in naming conventions, particularly because the origin of a given object cannot usually be determined. The proposal to rename the lowest mass brown dwarfs "isolated planets" only confuses the problem of understanding the origin and properties of objects in the overlapping mass region.

The deuterium burning limit (13 M_J) has been proposed as a nomenclature cutoff, but this limit has no long-term evolutionary effects, nor (based on the observed mass distributions) does it have much to do with the formation of brown dwarfs or planets. If two classes of objects overlap in mass space, these classes of "brown dwarfs" and "planets" will likely have different statistical properties that will allow them to be distinguished.

The similarity of the observed properties of more massive brown dwarfs to stars has linked them to star formation. Extension of the studies of the initial mass function, binary frequency, disk frequency, magnetic fields, rotation, composition, and other parameters to lighter objects (<20 M_J) now promises to reveal important insights into the differences between brown dwarfs and giant planets.

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PERSPECTIVES: CLIMATE CHANGE

How Fast Are Sea Levels Rising?

John A. Church

Sea levels are expected to rise as a result of global warming, with adverse effects on many people living in coastal areas. Accurate projections of sea level rise are therefore important for guiding policy. However, the most recent Intergovernmental Panel on Climate Change (IPCC) assessment of sea level rise (*1*) shows that the average of model estimates of 20th century sea level rise is low compared to the observations and there is a large range (1 to 2 mm/year) of observational estimates.

It is important that the observational and model estimates are reconciled. If the 20th century model estimates are low, then projections for the 21st century may also be underestimated. Alternatively, the observational estimates of 20th century sea level rise may be too high. This is the conclusion reached by Cabanes *et al.* on page 840 of this issue (*2*). The authors examine global altimeter and ocean temperature observations and arrive at observational estimates of sea level rise that are closer to the model estimates.

Several factors contribute to sea level change. The most important contribution to 20th and 21st century sea level rise is likely to be thermal expansion of the ocean as it warms. Other contributions include the melting of glaciers, changes in the mass of the Antarctic and Greenland ice sheets, and (highly uncertain) changes in the terrestrial storage of water.

Observational estimates of sea level change are based on the short (less than 10 years) satellite record of sea level height and the longer but geographically uneven and sparse tide-gauge network. The latter has few gauges with long records in the ocean-dominated Southern Hemisphere and few gauges at mid-ocean locations. Other difficulties in determining the rate of 20th century sea level change include the need to allow for land motions (both post-glacial rebound and tectonic motions) and for regional differences in sea level rise.

Regional differences in the rate of sea level rise should leave a mark in the pattern

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